NSABP
National Surgical Adjuvant Breast and Bowel Project

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Larry G. Hart, M.D.
111 Alexander Drive
Building 101 Research
Triangle Park, NC 27709

Dear Dr. Hart:

It is my understanding that the National Toxicology Program Board of Scientific Counselors will be holding a public meeting on October 30 and 31, 1997 to discuss the possible listing of Tamoxifen for the 9th Report on Carcinogens. I would like to take the opportunity to alert the board to an ongoing study that may influence their decision.

In June of 1992, the National Surgical Adjuvant Breast and Bowel Project (NSABP) an NCI-funded cooperative trials group began Protocol P-1, A Clinical Trial to Determine the Worth of Tamoxifen for Preventing Breast Cancer. This is a randomized, Phase III, double-blind trial that completed the accrual phase on September 30, 1997 with 13,388 women randomized into the trial. These are otherwise healthy individuals who have an increased risk for the future development of breast cancer, but at the present time, have no evidence of the disease. Prior to entry, all women were required to have a gynecologic examination and to have an annual gynecologic examination for the duration of the study. In addition, if they develop postmenopausal vaginal bleeding or irregular menstrual periods, they are instructed to have gynecologic examinations at that time. At each gynecologic visit, they have been strongly encouraged to undergo endometrial sampling. In 1994, the protocol entry criteria were modified to require endometrial sampling prior to randomization. Tamoxifen or placebo is administered for a 5-year period, and the participants are seen at 6-month intervals. At each of these non-gynecologic visits, they are to be questioned about the development of any tamoxifen-related symptoms, but particularly, symptoms of endometrial cancer.

Data on all gynecologic procedures, as well as all cancers, including breast, genitourinary, and gastrointestinal malignancies, are tracked centrally at the NSABP Biostatistical Center in Pittsburgh. The trial is reviewed by an independent data monitoring committee comprised of leading experts in the fields of Oncology, Gynecology, Cardiology, Biostatistics, and Bioethics. It is anticipated that the results of this trial, both the benefits and risks, will be available within the next 2 years. As a result of these study requirements and procedures, the data from NSABP Protocol P-1 are likely to provide a prospective assessment of the risks and benefits of tamoxifen therapy in a manner and magnitude not currently available.

Brian MacMahon, in his paper "Overview of Studies on Endometrial Cancer and Other Types of Cancer in Humans: Perspectives of an Epidemiologist", published in the *Seminars in Oncology*, Volume 24, Number 1, Supplement 1, describes the evidence of an association between endometrial cancer and tamoxifen as "far from conclusive". It is my personal experience that when tamoxifen was named as a carcinogen by other state or international review bodies, and subsequently reported in the media, that a substantial number of women taking tamoxifen for the treatment of breast cancer simply discontinued the therapy without consulting their physician to obtain appropriate guidance in the matter. Tamoxifen has clearly established value in the treatment of breast cancer and stopping the medication solely in reaction to news reports is not in any patient's best interest. I would recommend to the Board of Scientific Counselors that they delay their decision concerning classifying tamoxifen as a carcinogen until the results of NSABP Protocol P-1 are available to better guide their decision-making process.

Sincerely,

D. Lawrence Wickerham

D. Lawrence Wickerham, M.D.
Associate Chairman

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